Direct dehydrative cross-coupling of tautomerizable heterocycles with alkynes *via* Pd/Cu-catalyzed phosphonium coupling[†][‡]

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The first chemoselective direct dehydrative cross-coupling of tautomerizable heterocycles with alkynes has been achieved *via* C–H/C–OH bond activations with direct $C(sp^2)$ –C(sp) bond formation, which is in line with ideal synthesis using readily available materials.

Organic synthesis is the art and science of molecular engineering. "What for? From what? How?" are constant challenges that motivate synthetic chemists¹ in the development of ideal syntheses to advance life and material sciences. "Ideal synthesis" is defined as green, efficient and atom-economic processes that generate products in high yields using readily available materials with minimal wastes.² Readily available materials are inexpensive, inert, unactivated and unprotected (IIUU) molecules, which are in contrast to the conventional expensive, reactive, activated and protected intermediates in traditional synthesis.

Carbon–carbon (C–C) bond formation plays a central role in organic synthesis.³ Metal-catalyzed cross-coupling reactions for C–C bond formations are important components in the modern chemical technology toolbox. Traditional demetal halide cross-couplings⁴ (Scheme 1) have been indispensable methodologies to effect C–C bond formation from small-scale synthesis in drug discovery to large-scale manufacture of commercial medicines. These technologies, however, often involve the coupling of activated carbon–halogen (C–X) and carbon–metal (C–M) intermediates. Preparation of these chemically reactive and usually unstable intermediates normally requires multiple steps, which are not only expensive, but also generate wastes.

In recent years, development of direct cross-couplings, such as dehydrohalide,⁵ demetal hydride⁶ and demetal hydroxide⁷ cross-couplings, have received considerable attention. These new technologies replace one of the expensive unstable coupling partners (C–X or C–M) with IIUU molecules, and enable the C–C bond formations *via* C–H or C–OH bond activations. Therefore, direct cross-couplings are becoming highly attractive approaches in terms of efficiency, economy and environmental impact.

The state of the art of direct cross-couplings in ideal synthesis is arguably the coupling of two IIUU molecules, in which a C–C bond formation between them does not occur until a catalyst and an additive are added into the reaction.

Traditional demetalhalide cross-coupling



Scheme 1 Traditional vs. direct cross-couplings.

The key in designing such a novel process relies on the unique combination of catalysts and additives, which should not only chemoselectively and regioselectively activate and merge the two molecules, but also maintain an efficient catalytic cycle under mild conditions. To this end, direct dehydrogenative cross-couplings⁸ have recently emerged as promising and powerful technologies for C–C bond formations. These reactions employ two IIUU molecules *via* C–H/C–H bond activations in the presence of a catalyst (metal salt) and an additive (oxidant). Another conceptually similar approach is the direct dehydrative cross-coupling between two IIUU molecules *via* C–H/C–OH bond activations. Herein, we report the first chemoselective direct dehydrative cross-coupling of tautomerizable heterocycles with alkynes *via* Pd/Cu-catalyzed phosphonium coupling.

Phosphonium coupling is a mild efficient chemoselective and versatile methodology for the direct C–C, C–N, C–O and C–S bond formations of tautomerizable heterocycles.^{7,9} It proceeds through *in situ* C–OH bond activation of a tautomerizable heterocycle with a phosphonium reagent, *e.g.* PyBroP (bromotris(pyrrolidino)phosphonium hexafluorophosphate),^{7,9} followed by subsequent functionalization of the *in situ* formed "pseudo-aryl halide"^{9,c,10} with either a nucleophile

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Table 1 Screening of conditions



^{*a*} Condition A: 2-quinoxalinone (0.5 mmol), PyBroP (1.2 eq) and Et₃N (6 eq) in 1,4-dioxane (5 mL), then *p*-tolylacetylene (2 eq) and base (1.5 eq) at r.t. for 18 h. ^{*b*} Condition B: 2-quinoxalinone (0.5 mmol), PyBroP (1.2 eq) and Et₃N (6 eq) in 1,4-dioxane (5 mL), then *p*-tolylacetylene (2 eq), Pd catalyst and/or CuI at r.t. for 18 h.

through S_NAr displacement or an organometallic through metalcatalyzed cross-coupling. Its featured operational simplicity, functionality compatibility, broad substrate scope, and protectinggroup-free synthesis¹¹ have led to the facile access to many biologically important heterocyclic compounds in recent years.^{9c}

As phosphonium coupling has addressed direct $C(sp^2)-C(sp^3)$ and $C(sp^2)-C(sp^2)$ bond formations,^{7,9} we envisioned that it could also enable direct $C(sp^2)-C(sp)$ bond formation *via* direct dehydrative cross-coupling between tautomerizable heterocycles and alkynes, which are both typical IIUU molecules. Direct dehydrative cross-coupling of 2-quinoxalinone and *p*-tolylacetylene was studied under various base-promoted (Et₃N, NaOBu¹) and metal-catalyzed (Pd, Cu, Pd–Cu) phosphonium coupling conditions at room temperature (Table 1). No coupling products were observed under the based-promoted or Cu-catalyzed conditions. However, the Cu-free Pd-catalyzed reaction was found to undergo slowly with low conversion. Interestingly, we found that direct dehydrative cross-coupling indeed proceeded rapidly under the Pd/Cu-catalyzed condition producing 2-*p*-tolylethynylquinoxaline in high yield.¹²

It is noteworthy that decrease of the catalyst loading from 5/10 mol% (Pd/Cu) to 1/2 mol% (Pd/Cu) (Table 1, entries 6 and 7) led to comparable results. Screening of various Pd catalysts suggested that PdCl₂(PPh₃)₂ was more effective than other tested catalysts, which was also found to be the preferred catalyst in the Pd-catalyzed direct arylation of tautomerizable heterocycles with aryl boronic acids.⁷ As shown in this study as well as in the previous study, the *in situ* "pre-formation" of the heterocycle–phosphonium intermediate is not necessary.¹³ Hence, the catalysts and the additive can be added together along with the starting materials. In practice, however, it always makes more mechanistic sense to add the additive (PyBroP) shortly before the catalysts (Pd/Cu), since it is the *in situ* formed heterocycle–phosphonium intermediate that initiates the subsequent cross-coupling reaction.



Entry	Ar–OH	RCC–H	Ar-CCR	Yield (%)
1	H N N	H-=-		78 ^a
2	H N N	нОМе	OMe OMe	80^a
3	H N N	HCF3	CF3	49, ^{<i>a</i>} 78 ^{<i>c</i>}
4	H N N	H\\$_]	N S	72 ^{<i>a</i>}
5	H N N	H		68 ^{<i>a</i>}
6	H N N	H	N Me	70 ^a
7	H N N	H	CI	82 ^{<i>a</i>}
8	H N N	нОН	OH	72 ^{<i>a</i>}
9	H N N	Н──── ^{Ме} Н────ОН Ме	Me OH Me	75 ^a
10	H N N	н	OH	70 ^{<i>a</i>}
11		HMe	NO ₂ Me	74 ^{<i>b</i>}
12	NH	HMe	Me	66 ^b
13	SNH	HMe	S New Me	70 ^b
14	S NH	HMe	CS Mo	72 ^b
15	Me N O EtO ₂ C N Ph	HMe	Me_N_Me Eto ₂ C_N	73 ^b

^{*a*} Condition A: ArOH (0.5 mmol), PyBroP (1.2 eq) and Et₃N (6 eq) in 1,4-dioxane (5 mL), then RCCH (2 eq), PdCl₂(PPh₃)₂ (5 mol%), CuI (10 mol%) at r.t. for 18 h. ^{*b*} Condition B: ArOH (0.5 mmol), PyBroP (1.2 eq) and Pri₂NEt (6 eq) in 1,4-dioxane (5 mL) at 50 °C for 2 h, then RCCH (2 eq), PdCl₂(PPh₃)₂ (5 mol%), CuI (10 mol%) at 80 °C for 18 h. ^{*c*} Condition C: ArOH (0.5 mmol), PyBroP (1.2 eq) and Et₃N (6 eq) in 1,4-dioxane (5 mL), then RCCH (2 eq), PdCl₂(PPh₃)₂ (5 mol%) (2 eq), PdCl₂(PPh₃)₂ (5 mol%), CuI (10 mol%) at 50 °C for 18 h.

Direct dehydrative cross-coupling of 2-quinoxalinone with other alkynes were subsequently investigated. We found that aryl alkynes, alkenyl alkynes, and alkyl alkynes all worked well in moderate to high yields at room temperature under ambient atmosphere using the Pd/Cu catalyzed condition. However, in the case of an electron-deficient alkyne, the Cu-free condition at 50 °C was found to give a higher yield (Table 2, entry 3). The unique chemoselectivity of this new methodology is clearly demonstrated in the direct cross-couplings involving the sensitive hydroxylated alkynes (Table 2, entries 8-10), which would be difficult to achieve using other existing technologies. Next, this new Pd/Cu-catalyzed phosphonium coupling was applied to other tautomerizable heterocycles with *p*-tolylacetylene. We found that the coupling reactions of these tautomerizable heterocycles appeared to be somewhat slower under the same conditions, probably due to their slightly different reactivity. We found that these reactions can be accelerated under the modified conditions using a slightly stronger base (*i*Pr₂NEt) at higher temperatures (50-80 °C).¹⁴

We proposed the possible mechanism of the direct dehydrative cross-coupling of 2-quinoxalinone with p-tolylacetylene via Pd/Cu-catalyzed phosphonium coupling (Scheme 2). It may involve the following seven-step cascade of two (Pd/Cu) catalytic cycles via C-H/C-OH bond activations: (1) tautomerization of 2-quinoxalinone to 2-quinoxalinol in the presence of Et_3N ; (2) activation of 2-quinoxalinol with PyBroP generating the heterocycle-phosphonium intermediate (C-OH bond activation); (3) oxidative insertion of Pd⁰ catalyst to the C-O bond of the heterocycle-phosphonium intermediate forming the heterocycle-Pd^{II}-phosphonium species: (4) chelation of Cu^I catalyst to *p*-tolylacetylene affording the alkyne-Cu^I π -complex (C–H bond activation); (5) abstraction of the alkynyl hydrogen by Et₃N furnishing the alkynyl-Cu^I species; (6) unprecedented transmetalation of the heterocycle-Pd^{II}-phosphonium species with the alkynyl-Cu^I species resulting in the alkynyl-Pd^{II}-heterocycle species with regeneration of the Cu^I catalyst and release of TTPA; and (7) reductive elimination of the alkynyl heterocycle product with regeneration of the Pd⁰ catalyst. Consequently, the



Scheme 2 Possible mechanism of the direct dehydrative cross-coupling.

direct dehydrative cross-coupling results in a new $C(sp^2)$ –C(sp) bond formation, where a "H₂O" is formally eliminated from the starting materials in this new process with the "O" ending up in TTPA and the two "H" in Et₃N·HX.

In conclusion, we have developed the first Pd/Cu-catalyzed phosphonium coupling for the first chemoselective direct dehydrative cross-coupling of tautomerizable heterocycles with alkynes *via* C–H/C–OH bond activations with direct $C(sp^2)$ –C(sp) bond formation, which is in line with ideal synthesis using readily available materials. The scope of this new methodology has been shown to tolerate a variety of tautomerizable heterocycles and alkynes, particularly substrates with sensitive hydroxyl groups. The mechanism of the direct dehydrative cross-coupling is proposed to proceed through a domino seven-step process of two (Pd/Cu) catalytic cycles *via* C–H/C–OH bond activations involving an unprecedented transmetalation of a heterocycle-Pd^{II}-phosphonium species with an alkynyl-Cu^I species.

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